Supplementary Materials:

Fig. S1. High correlations with antigens expressed in different systems

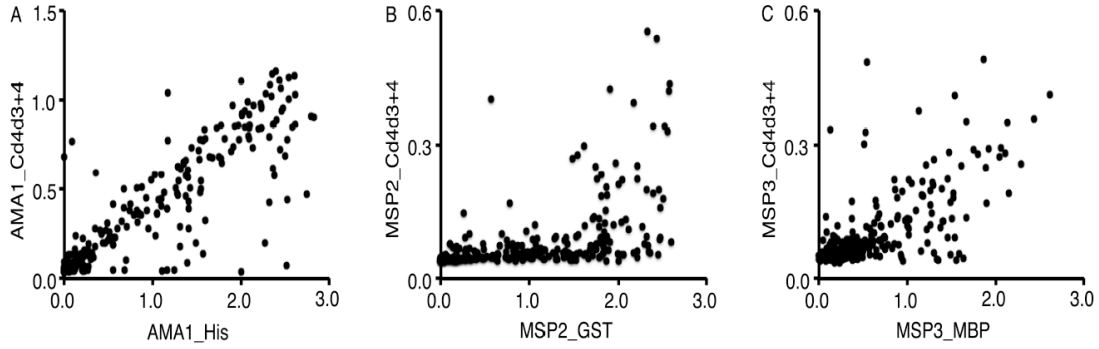


Fig. S1. High correlations with antigens expressed in different systems. Correlations between antibody reactivities against recombinant AMA1, MSP2 and MSP3 produced in the mammalian system versus those produced in *Escherichia coli.* All *E. coli* expressed antigens are considered to retain native conformation based on a range of experiments, including immuno-fluorescence assays. Antibody reactivities to **(A)** the 3D7 allele of AMA1; additionally, rabbit antibodies raised against this antigen were shown to inhibit parasite growth *in vitro* indicating it induced functional antibodies (*13*), **(B)** a type A MSP2 antigen (CH150/9)(*15*), and **(C)** the 3D7 allele of MSP3(*14*) are highly correlated with the same antigens based on the 3D7 allele from the protein library. Antibody reactivity data are taken from the Chonyi cohort (n = 286)(*16*).

Fig. S2. Low correlation between individual responses.

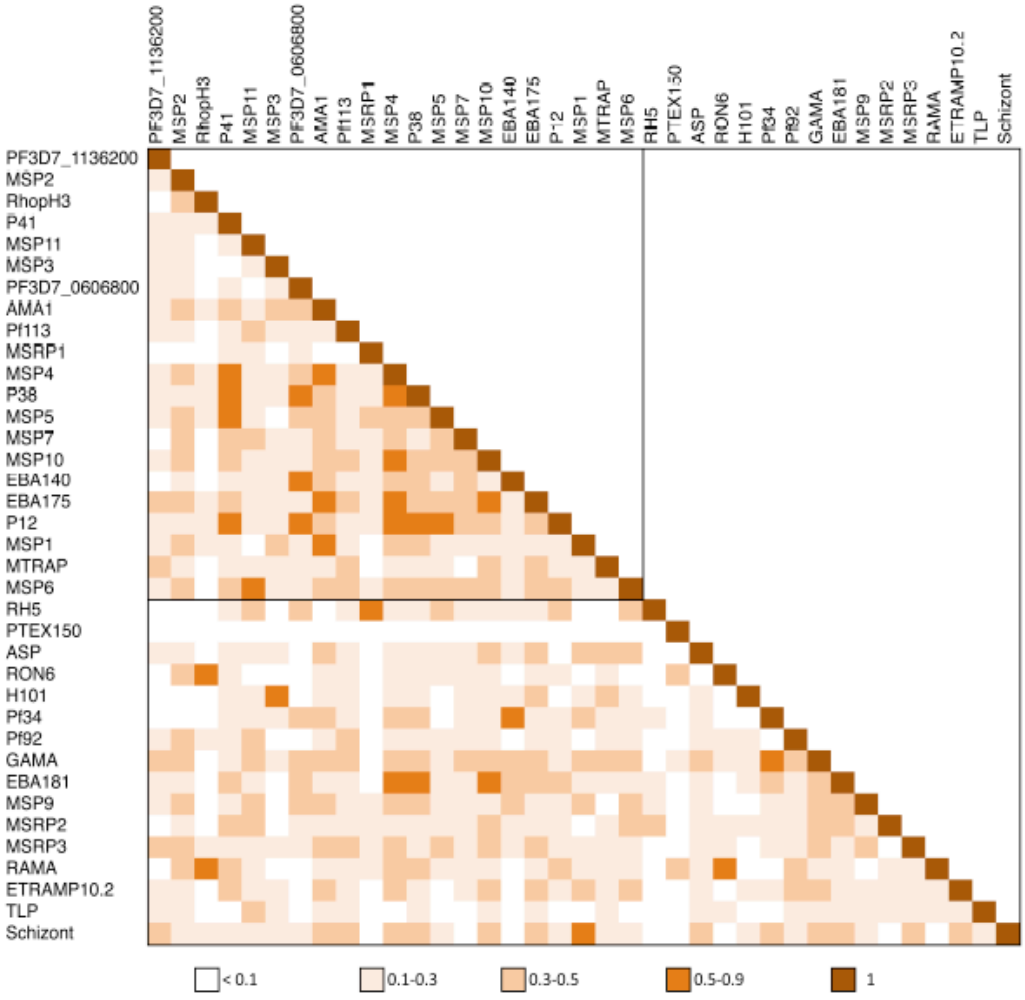


Fig. S2. Low correlation between individual responses. Pairwise correlation coefficients were calculated within the 121 parasite-positive children for all pairs of antibodies, including those against parasite schizont extract. Coefficients were ranked low, medium and high ($R < 0.3$; 0.3 - 0.5; 0.5 - 0.99, respectively), based on observed coefficients for allelic variants of the same antigen (see references in main text). Antigens were ranked according to their individual potential protective efficacy. The internal black lines separate protective from non-protective antigens.

Fig. S3. The breadth of the antibody response increases with age.

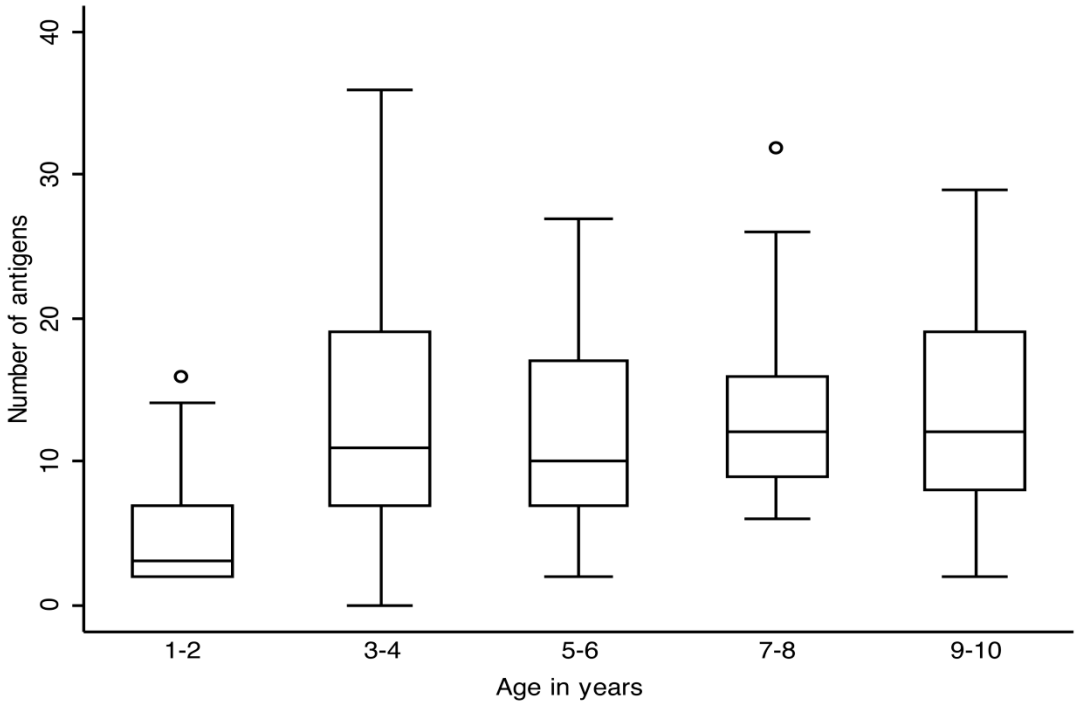
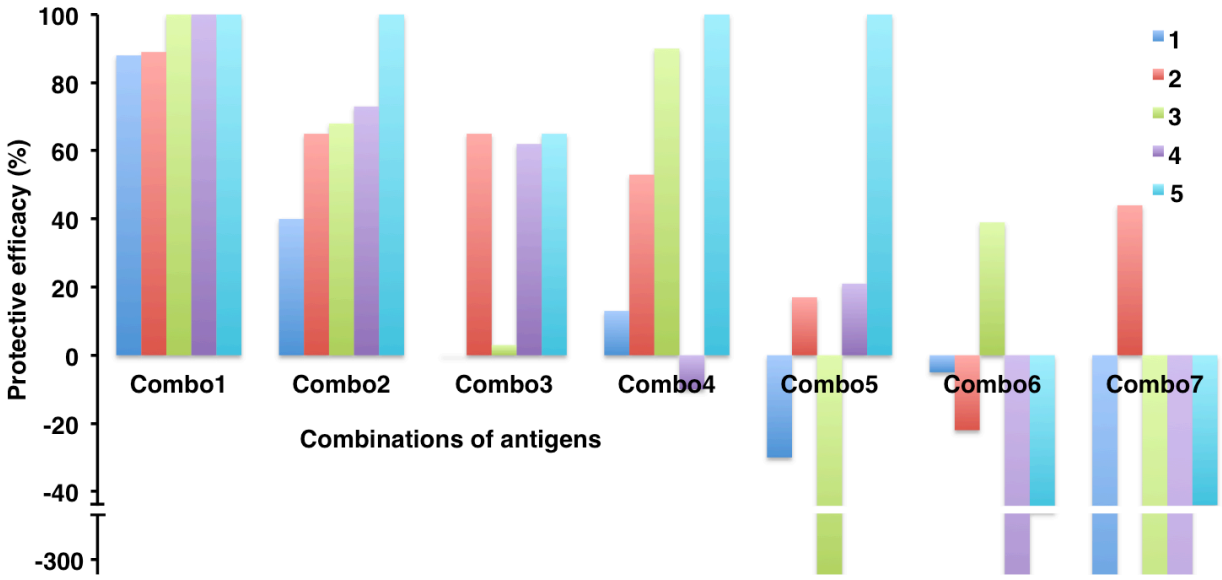


Fig. S3. The breadth of the antibody response increases with age.

The breadth score was defined as the sum of antibody responses against individual antigens within the library (coded 0=low/negative, 1=high/positive). Boxes show the median, 25th and 75th percentiles, whiskers show the upper and lower adjacent values. For each age category in ascending order, n = 56, 57, 55, 58 and 60, respectively.

Fig. S4. Selected responses in combination and protection: time to event analysis



Increasing breadth of responses to combinations of the most protective antigens is strongly associated with protection from malaria in a time to event analysis. The analyses are as presented in Figure 3B but with Hazard Ratios (HR) as the measure of risk. As in Figure 3B, "Combo1" contains the five individually most protective antibodies, "Combo2" the subsequent five etc. Combo7 contains the five least protective antigens, TLP was excluded.

Table S1. Antibody levels increase with age and parasitaemia

	ELISA OD	Level[a]		Prevalence[b]		Parasitaemia[c]	
Antigen	Median (Range)	Z	P	Z	P	Z	P
MSP1	0.37(0.04-1.13)	3.36	<0.01	1.89	0.06	5.58	<0.01
MSP2	0.05(0.03-0.55)	5.74	<0.01	3.81	<0.01	6.96	<0.01
MSP4	0.21(0.08-1.60)	7.46	<0.01	4.95	<0.01	6.29	<0.01
MSP5	0.08(0.04-0.48)	3.68	<0.01	3.29	<0.01	5.03	<0.01
MSP10	0.36(0.07-1.85)	6.74	<0.01	5.79	<0.01	6.52	<0.01
P12	0.08(0.06-0.63)	5.38	<0.01	3.46	<0.01	6.32	<0.01
P38	0.09(0.04-1.24)	3.37	<0.01	2.27	0.02	4.88	<0.01
Pf92	0.49(0.03-1.37)	7.46	<0.01	4.94	<0.01	4.93	<0.01
Pf113	0.05(0.05-0.38)	1.63	0.10	0.96	0.34	4.90	<0.01
PF3D7_1136200	0.06(0.04-0.19)	3.10	<0.01	2.27	0.02	4.56	<0.01
MSP3	0.06(0.03-0.65)	4.98	<0.01	5.10	<0.01	5.43	<0.01
MSP6	0.12(0.08-0.90)	5.67	<0.01	4.51	<0.01	7.70	<0.01
H101	0.04(0.04-0.66)	5.56	<0.01	1.87	0.06	6.33	<0.01
MSP11	0.05(0.03-0.39)	7.21	<0.01	6.10	<0.01	7.05	<0.01
MSP7	0.20(0.08-1.41)	7.95	<0.01	5.72	<0.01	8.04	<0.01
MSRP1	0.05(0.04-0.38)	5.20	<0.01	3.89	<0.01	7.79	<0.01
MSRP2	0.05(0.04-0.33)	4.78	<0.01	3.00	<0.01	5.89	<0.01
MSRP3	0.04(0.03-0.24)	3.31	<0.01	-2.17	0.03	4.50	<0.01
P41	0.05(0.03-1.14)	5.15	<0.01	4.50	<0.01	6.84	<0.01
MSP9	0.06(0.03-0.55)	4.60	<0.01	3.34	<0.01	6.27	<0.01
AMA1	0.19(0.03-1.15)	5.25	<0.01	2.81	<0.01	6.44	<0.01

EBA140	0.17(0.08-1.74)	5.95	<0.01	5.17	<0.01	4.80	<0.01
EBA175	0.15(0.08-1.94)	6.41	<0.01	5.84	<0.01	5.40	<0.01
EBA181	0.15(0.07-1.72)	4.77	<0.01	3.95	<0.01	4.14	<0.01
ASP	0.08(0.08-0.24)	6.35	<0.01	3.42	<0.01	6.98	<0.01
MTRAP	0.04(0.03-0.23)	5.37	<0.01	2.51	0.01	6.21	<0.01
GAMA	0.04(0.03-0.20)	5.11	<0.01	3.48	<0.01	5.89	<0.01
RH5	0.11(0.07-1.40)	7.19	<0.01	4.70	<0.01	5.40	<0.01
RhopH3	0.04(0.03-0.44)	2.87	<0.01	-2.26	0.02	1.41	0.16
Pf34	0.06(0.03-0.19)	6.64	<0.01	6.50	<0.01	5.46	<0.01
RON6	0.04(0.03-0.19)	3.13	<0.01	1.75	0.08	4.92	<0.01
RAMA	0.05(0.03-0.19)	1.98	0.05	1.17	0.24	4.22	<0.01
TLP	0.04(0.04-0.10)	1.01	0.31	1.25	0.21	2.56	0.01
PTEX150	0.07(0.05-0.71)	4.70	<0.01	3.20	<0.01	7.16	<0.01
ETRAMP10.2	0.04(0.04-0.10)	2.10	0.04	0.68	0.49	3.83	<0.01
PF3D7_0606800	0.06(0.03-0.68)	5.79	<0.01	5.98	<0.01	6.70	<0.01

Table S1. The Cuzick rank sum non-parametric test for trend across ordered groups was used to test whether ELISA OD reactivities (levels) increased with age[a], whether sero-prevalence increased with age[b], and whether parasite-positive children (n = 121) had higher ELISA OD reactivities than parasite-negative children[c] (n = 165). Age was analyzed in two-year categories, with n = 56, 57, 55, 58 and 60 for each category, respectively. Results are shown as Z statistics and P values.

Table S2. Responses to individual antigens and protection from malaria in parasite negative children

Rank	Antigen	Prevalence[a] (%)	RR(95% CI)	P value
1	PF3D7_1136200[c]	7	1.31(0.37-4.53)	0.67
2	MSP2	8	1.72(0.72-4.11)	0.22
3	RhopH3[c]	5	0.68(0.10-4.57)	0.69
4	P41	11	0.92(0.29-2.84)	0.89
5	MSP11	12	1.04(0.35-3.06)	0.93
6	MSP3	17	1.82(0.94-3.54)	0.07
7	PF3D7_0606800	14	0.99(0.43-2.29)	0.99
8	AMA1	20	1.81(0.85-3.86)	0.12
9	Pf113[c]	40	1.78(0.87-3.63)	0.11
10	MSRP1	10	0.80(0.20-3.14)	0.75
11	MSP4	18	1.02(0.45-2.31)	0.94
12	P38	16	1.59(0.68-3.71)	0.28
13	MSP5	23	0.75(0.34-1.65)	0.48
14	MSP7	12	0.99(0.36-2.74)	0.99
15	MSP10	21	1.67(0.80-3.50)	0.17
16	EBA140	14	0.71(0.22-2.31)	0.58
17	EBA175	15	1.93(0.89-4.20)	0.09
18	P12	15	1.40(0.61-3.19)	0.42
19	MSP1	24	1.46(0.72-2.97)	0.28
20	MTRAP[c]	15	1.21(0.59-2.47)	0.59

21	MSP6	10	0.84(0.24-2.90)	0.79
22	RH5[c]	18	0.93(0.37-2.27)	0.58
23	PTEX150[c]	16	0.43(0.10-1.75)	0.24
24	ASP[c]	12	0.55(0.15-2.01)	0.37
25	RON6[c]	23	0.83(0.34-2.04)	0.70
26	H101[c]	4	0.70(0.08-5.56)	0.74
27	Pf34[c]	41	0.91(0.45-1.85)	0.81
28	Pf92	31	1.13(0.51-2.50)	0.76
29	GAMA[c]	14	0.46(0.10-1.98)	0.30
30	EBA181	11	1.22(0.45-3.30)	0.68
31	MSP9	26	1.35(0.63-2.86)	0.43
32	MSRP2[c]	19	1.09(0.51-2.32)	0.82
33	MSRP3[c]	12	0.68(0.16-2.76)	0.58
34	RAMA[c]	33	0.50(0.21-1.19)	0.12
35	ETRAMP10.2[c]	5	1.69(0.29-9.75)	0.55
36	TLP[c]	7	0.65(0.19-2.21)	0.50

Table S2. Associations between responses to individual antigens and the risk of malaria were analyzed using modified binomial regression models in children who were parasite negative at screening (n=165). Data are presented as Risk Ratios (RR) with 95% Confidence intervals (95% CI), and are adjusted for age and reactivity to parasite schizont extract. [a]Prevalence of high titer responses. [c]Seropositivity used for analysis (see Methods).

Table S3. Responses to individual antigens and protection from malaria in a time to event analysis

Rank	Antigen	Prevalence[a] (%)	HR(95% CI)	P value
1	PF3D7_1136200[c]	12	0.10(0.01-0.79)	0.03*
2	RhopH3[c]	7	0.17(0.04-0.77)	0.02*
3	MSP2	27	0.24(0.08-0.69)	0.01*
4	MSP11	38	0.38(0.16-0.89)	0.03*
5	P41	32	0.39(0.15-0.99)	0.05*
6	MSRP1	21	0.44(0.21-0.91)	0.03*
7	AMA1	48	0.45(0.21-0.99)	0.05*
8	MSP3	31	0.55(0.24-1.28)	0.17
9	PF3D7_0606800	36	0.59(0.27-1.20)	0.17
10	MSP7	46	0.61(0.29-1.30)	0.21
11	MSP4	41	0.62(0.27-1.42)	0.26
12	Pf113[c]	63	0.63(0.32-1.24)	0.19
13	P38	35	0.63(0.28-1.42)	0.27
14	MSP5	43	0.63(0.30-1.31)	0.22
15	EBA175	31	0.65(0.26-1.64)	0.37
16	RH5[c]	48	0.66(0.32-1.36)	0.27
17	MSP10	47	0.67(0.32-1.37)	0.28
18	EBA140	25	0.68(0.25-1.89)	0.47
19	ETRAMP10.2[c]	8	0.71(0.21-2.40)	0.59
20	P12	40	0.77(0.36-1.64)	0.51

21	MSP6	34	0.77(0.35-1.69)	0.52
22	MTRAP[c]	27	0.78(0.40-1.52)	0.46
23	MSP1	51	0.80(0.37-1.71)	0.57
24	ASP[c]	29	0.90(0.37-2.21)	0.83
25	RON6[c]	39	0.97(0.50-1.88)	0.95
26	H101[c]	17	0.97(0.36-2.59)	0.95
27	Pf92	53	0.99(0.46-2.31)	0.98
28	PTEX150[c]	48	1.13(0.58-2.19)	0.71
29	MSRP3[c]	12	1.14(0.47-2.75)	0.76
30	RAMA[c]	56	1.19(0.60-2.36)	0.62
31	EBA181	26	1.25(0.50-3.10)	0.62
32	Pf34[c]	70	1.33(0.63-2.83)	0.45
33	GAMA[c]	31	1.34(0.62-2.85)	0.45
34	MSRP2[c]	45	1.40(0.71-2.74)	0.33
35	TLP[c]	18	1.41(0.60-3.28)	0.43
36	MSP9	36	1.43(0.68-3.01)	0.34

Table S3. Associations between responses to individual antigens and the risk of malaria were analyzed using modified binomial regression models in children who were parasite negative at screening (n=165). Data are presented as Hazard Ratios (HR) with 95% Confidence intervals (95% CI), and are adjusted for age and reactivity to parasite schizont extract. [a]Prevalence of high titer responses. [c]Seropositivity used for analysis (see Methods). None of the associations remained significant after adjusting for multiple testing.